ORIGINAL RESEARCH

Thromboembolic Events Associated with Bevacizumab plus Chemotherapy for Patients with Colorectal Cancer: A Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Bevacizumab is a recombinant, humanized monoclonal antibody that hinders the proliferation of new blood vessels required for malignant progression. The drug is considered safe and tolerable; however, some controversy remains about whether it is linked to venous and arterial thromboembolic events (TEEs).

OBJECTIVE: To evaluate the risk for overall, venous, and arterial TEEs in patients with colorectal cancer (CRC) who are administered bevacizumab plus chemotherapy in randomized controlled trials (RCTs).

METHODS: We searched PubMed and CENTRAL databases to extract reports of relevant trials that were published in English between January 1, 2003, and December 31, 2014. All RCTs in which bevacizumab plus chemotherapy was compared with standard chemotherapy or with placebo plus chemotherapy for the treatment of CRC, and TEEs were reported, were included in a meta-analysis. Risk ratios (RRs) with 95% confidence intervals (CIs) of TEEs were calculated for each RCT. Because the between-study heterogeneities (I^2) were insignificant, a fixed-effect model was used to determine the effect size of each TEE. A funnel plot was created to assess publication bias, and 2 forms of sensitivity analyses were performed for each outcome.

RESULTS: This meta-analysis included 22 RCTs with a total of 13,185 patients. Overall, compared with the control groups, patients with CRC who received bevacizumab were at significant risk for overall TEEs (RR, 1.334; 95% CI, 1.191-1.494; P <.001; I^2 = 1.37%). Regarding venous TEEs, a significant risk was observed for patients who received bevacizumab versus control patients (RR, 1.244; 95% CI, 1.091-1.415; P = .001; I^2 = 0.0%). Similarly, the risk for arterial TEEs was significant in bevacizumab-treated patients (RR, 1.627; 95% CI, 1.162-2.279; P = .005; I^2 = 0.0%). Sensitivity analyses did not affect the level of significance of the effect size for each outcome, and no significant publication bias was observed.

CONCLUSION: In all the studies reviewed in this meta-analysis, the risk for venous or arterial TEEs was associated with bevacizumab use in patients with CRC. Healthcare providers are encouraged to consider thromboprophylaxis agents, periodically monitor their patients who receive bevacizumab, and carefully manage patients who are at increased risk for those complications.

Stakeholder Perspective, page 232

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KEY WORDS: arterial thromboembolic events, bevacizumab, colorectal cancer, meta-analysis, randomized controlled trials, TEEs, venous thromboembolic events

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Bevacizumab (Avastin) is a recombinant, humanized monoclonal antibody known as antiangiogenic or anti–vascular endothelial growth factor (anti-VEGF), which has a unique mechanism of action. It works through blocking the angiogenesis process, a physiologic process leading to the generation of new blood vessels, by targeting the VEGF.[1-5] Those blood vessels are the source of oxygen, blood, and nutrition needed for the

KEY POINTS

- Bevacizumab is considered safe, but questions remain about whether it increases the risk for venous and arterial thromboembolic events (TEEs).
- In this new meta-analysis, the authors evaluated randomized controlled trials (RCTs) to consider whether patients with CRC who receive bevacizumab plus chemotherapy are at increased risk for such events.
- The analysis included 22 RCTs comparing bevacizumab plus chemotherapy and a control treatment in patients with CRC; a total of 13,185 patients were included in the analysis.
- Compared with the control groups, patients with CRC who received bevacizumab were at significant risk for overall TEEs, including arterial and venous TEEs.
- Providers may need to consider thromboprophylaxis in patients with CRC who receive bevacizumab, and carefully monitor and manage patients who are at risk for TEEs.

progression of most malignant cells; by hindering their proliferation, a progression-free state is ensured.[4]

In 2004, the US Food and Drug Administration granted the first approval of bevacizumab for use in multiple metastatic cancers. In the same year, bevacizumab was approved as first-line treatment in combination with other chemotherapies for metastatic colorectal cancer (CRC).[6,7] Currently, bevacizumab is one of the most used antiangiogenic drugs for patients with CRC.

A study by Hess and colleagues indicated that more than 68% of patients with metastatic CRC in the United States were exposed to bevacizumab from 2004 to 2008.[8] More precisely, bevacizumab was prescribed for 901 (54%) of 1655 patients with metastatic CRC as initial first-line treatment, for 58% of those who needed a continued second-line regimen, and for 50% of those who were administered third-line therapy.[8] In addition, bevacizumab was prescribed for 57% of geriatric patients with newly diagnosed CRC and for 44% of geriatric patients with relapsed CRC.[9]

Previous clinical trials have proved that adding bevacizumab to the traditional chemotherapy regimens for metastatic CRC, as either a first- or second-line drug, has led to significant improvement in the rates of response,[10-13] overall survival,[12-14] and progression-free survival[15-18] compared with chemotherapy alone. However, the majority of those reports show that bevacizumab has been associated with an increased risk for serious adverse events. Most of those adverse events ranged from mild to moderate in severity and were common (eg, high blood pressure, bleeding, constipation, thrombocytopenia, proteinuria, bowel perforation).[11-32] Thromboembolic events (TEEs) were generally rare in the bevacizumab-treated population, yet were life-threatening and warrant careful monitoring and management.[11-32]

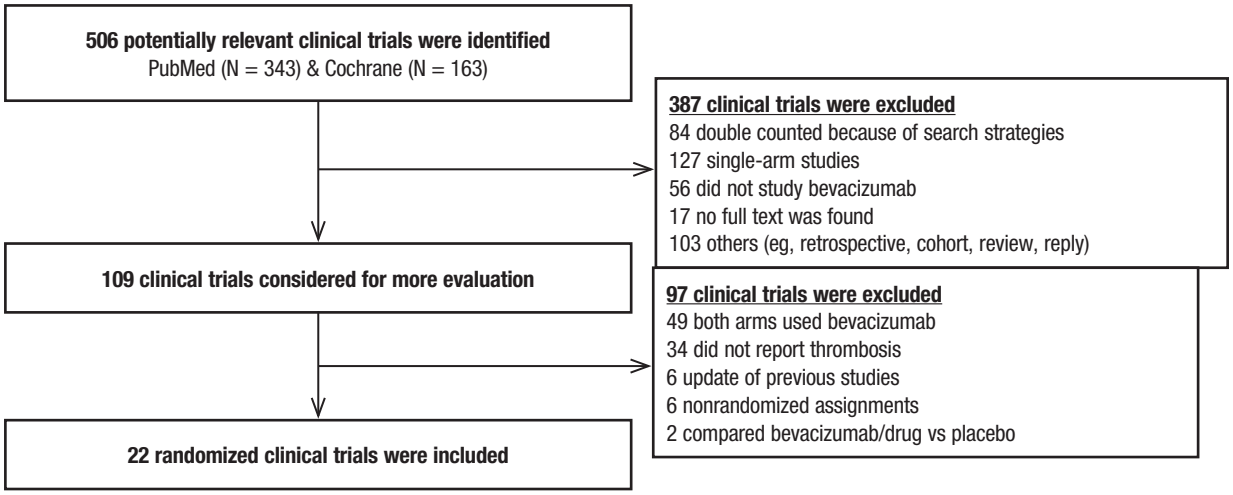
Bevacizumab has shown superiority in improving overall survival for patients with cancer, but because the increased risk for TEEs leads to higher mortality, such superiority may be affected.[3,33-38] In previous meta-analyses, the incidence of arterial and venous TEEs among patients with different types of cancer treated with bevacizumab ranged from 0.6% to 5.6%[34,35,37,38] and from 6.8% to 19.9%,[33] respectively; among patients with CRC, the incidence of these events ranged from 0.5% to 8.5%[34,35,37,38] and from 16.1% to 22.6%,[33] respectively.

Complications such as thrombosis have been linked to cancer for many years, and thrombosis was ranked second in the list of causes of death among patients with cancer.[39] By contrast, cancer is one of the main risk factors leading to venous TEEs, and it had been estimated that approximately 20% of all venous TEEs were cancer-related.[40,41] Along with medications, the risk for TEEs is influenced by many cofactors, such as age, trauma, smoking status, surgery, immobility, blood abnormalities, cancer and its type, hormonal therapy, and pregnancy.[41,42] Previous epidemiologic studies demonstrated that the risk for TEEs varied by type of cancer. Compared with cancer-free patients, individuals with brain cancer and those with colon cancer are at an increased relative risk for TEEs, >25% and >17%, respectively.[41,43]

Previous meta-analyses have tried to determine the risk for either arterial or venous TEEs associated with bevacizumab use in patients with cancer.[33-38] Scappaticci and colleagues analyzed 5 randomized controlled trials (RCTs) and found a significantly greater risk for arterial but not for venous TEEs among various cancers.[34] A pooled analysis of 15 RCTs showed a significant risk for venous TEEs among all patients with cancer but a nonsignificant risk for patients with CRC.[33] In contrast, the analysis of 10 RCTs by Hurwitz and colleagues showed a nonsignificant risk for venous TEEs among all patients with cancer, including those with CRC.[36]

Other studies indicated that the risk for arterial TEEs is significant for patients with all types of cancer, including CRC.[35,37,38] However, those studies have some limitations. First, the goal of those studies was to investigate the risk for TEEs by analyzing RCTs of various types of cancers rather than just one type. It would be more reliable to examine the association between each cancer and TEEs, which would minimize the confounding effects of cancer type and site. Furthermore, those studies

Figure 1 Selection Diagram for Randomized Controlled Trials in This Study



were limited to few RCTs and a small sample size for each type of cancer, which might have led to underestimation of the true risk for TEEs.

Other studies investigated the safety of bevacizumab in patients with CRC.[44-49] Although 5 studies showed that bevacizumab use was associated with a significant risk for thrombosis, no detailed results for arterial or venous TEEs were presented.[44-48] In contrast, a study by Galfrascoli and colleagues shows a significant risk for arterial TEEs but a nonsignificant risk for venous thrombosis in the bevacizumab group.[49]

Given the association between chemotherapy and TEEs, the high mortality rate caused by cancer-related thrombosis, and the conflicting results of published studies, a meta-analysis to address the risk for TEEs in patients with CRC is needed to enhance healthcare providers' awareness and inform careful patient management. In previous meta-analyses, the risk for thrombosis associated with bevacizumab use was examined among patients with different types of cancer, including CRC. However, there is no recent and large meta-analysis in which this association was analyzed solely for patients with CRC. Therefore, the objective of the current meta-analysis was to determine the risk for overall, venous, and arterial TEEs associated with bevacizumab plus chemotherapy in patients with CRC.

Methods

Search Strategy

To identify and extract relevant clinical trials, we performed a comprehensive literature search using the databases of PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL).

In PubMed, this search was limited to RCTs whose title and abstract contained all the following key words—"bevacizumab" and "colorectal cancer," "bevacizumab" and "colon cancer," "bevacizumab" and "rectal cancer," "Avastin" and "colorectal cancer," "Avastin" and "colon cancer," "Avastin" and "rectal cancer," "antiangiogenic" and "colorectal cancer," "antiangiogenic" and "colon cancer," "antiangiogenic" and "rectal cancer," "anti-VEGF" and "colorectal cancer," "anti-VEGF" and "colon cancer," and "anti-VEGF" and "rectal cancer." In addition, we conducted a PubMed search limited to abstracts only, using pairs of the key words, "bevacizumab" and "thrombosis," "bevacizumab" and "thromboembolism," "bevacizumab" and "thrombotic," "bevacizumab" and "embolism," "bevacizumab" and "infarction," and "bevacizumab" and "ischemia."

For the CENTRAL database, the search was limited to title, abstract, and the key word combinations of "bevacizumab," "colorectal cancer," and "clinical trials"; "bevacizumab," "colon cancer," and "clinical trials"; "bevacizumab," "rectal cancer," and "clinical trials"; "Avastin," "colorectal cancer," and "clinical trials"; "Avastin," "colon cancer," and "clinical trials"; and "Avastin," "rectal cancer," and "clinical trials."

These searches were restricted to clinical trials in humans that were published between January 1, 2003, and December 31, 2014, and were written in English. We searched the references cited in the retrieved studies, but have not contacted any of the authors of those studies.

Inclusion/Exclusion Criteria

To achieve our objective, only RCTs that involved humans and comparisons of bevacizumab with a standard

Table Overview of the 22 Randomized Controlled Trials with Bevacizumab for Colorectal Cancer

Clinical trial	Trial phase	Cancer stage	Treatment arm and bevacizumab dose			Study sample size	Follow-up duration, mo	Quality score
			Control arm	Treatment arm	Bevacizumab dose			
Kabbinavar et al 2003[11]	2	mCRC	Fluorouracil and leucovorin	Fluorouracil, leucovorin, + bevacizumab	5 mg/kg or 10 mg/kg × 2 wks	104	12	2
Hurwitz et al 2004[12]	3	mCRC	IFL + placebo	IFL + bevacizumab	5 mg/kg × 2 wks	813	24	3
Kabbinavar et al 2005[19]	2	mCRC	Fluorouracil and leucovorin + placebo	Fluorouracil and leucovorin + bevacizumab	5 mg/kg × 2 wks	209	24	3
Giantonio et al 2007[13]	3	mCRC	Oxaliplatin, fluorouracil, + leucovorin	Oxaliplatin, fluorouracil, and leucovorin + bevacizumab	10 mg/kg × 2 wks	289	28	3
Saltz et al 2008[20]	3	mCRC	FOLFOX4 or XELOX + placebo	FOLFOX4 or XELOX + bevacizumab	5 mg/kg × 2 wks or 7.5 mg/kg × 3 wks	1400	12	3
Hochster et al 2008[21]	NA	mCRC	mFOLFOX6 or bFOL or CapeOx	mFOLFOX6 + bevacizumab or bFOL + bevacizumab or CapeOx + bevacizumab	5 mg/kg × 2 wks or 7.5 mg/kg × 3 wks	360	15-18	3
Jackson et al 2009[22]	3	mCRC	FOLFIRI or mIFL	FOLFIRI + bevacizumab or mIFL + bevacizumab	5 mg/kg × 2 wks or 7.5 mg/kg × 3 wks	389	23-34	2
Sharma et al 2010[23]	2	mCRC	FOLFOX-axitinib	FOLFOX-axitinib + bevacizumab	5 mg/kg × 2 wks	10	1-16	2
Allegra et al 2009[14]	3	II or III	mFOLFOX6	mFOLFOX6 + bevacizumab	5 mg/kg × 2 wks	2710	12	2
Tebbutt et al 2010[16]	3	mCRC	Capecitabine	Capecitabine + bevacizumab	7.5 mg/kg × 3 wks	313	30.8	1
Kemeny et al 2011[24]	2	mCRC	Fluorodeoxyuridine, dexamethasone, and irinotecan or oxaliplatin, fluorouracil, + leucovorin	Fluorodeoxyuridine, dexamethasone, and irinotecan or oxaliplatin, fluorouracil, leucovorin, + bevacizumab	5 mg/kg × 2 wks	73	30	2
Madajewicz et al 2012[7]	2	Advanced CRC	FFG or FOLFOX4	FFG + bevacizumab or FOLFOX4 + bevacizumab	5 mg/kg × 2 wks	84	NA	1
Price et al 2012[17]	2/3	Advanced CRC	Capecitabine	Capecitabine + bevacizumab	NA	471	NA	1
Guan et al 2011[25]	3	mCRC	mIFL	mIFL + bevacizumab	5 mg/kg × 2 wks	211	NA	3
Stintzing et al 2012[26]	3	mCRC	FOLFIRI + cetuximab	FOLFIRI + bevacizumab	5 mg/kg × 2 wks	96	60	3
Bennouna et al 2013[27]	3	mCRC	Chemotherapy	Chemotherapy + bevacizumab	5 mg/kg × 2 wks or 7.5 mg/kg × 3 wks	820	10	3
de Gramont et al 2012[28]	3	II or III	Oxaliplatin, fluorouracil, + leucovorin	Oxaliplatin, fluorouracil, and leucovorin + bevacizumab	5-7.5 mg/kg × 3 wks	2306	48.5	3

(Continued)

Table Overview of the 22 Randomized Controlled Trials with Bevacizumab for Colorectal Cancer *(Continued)*

Clinical trial	Trial phase	Cancer stage	Treatment arm and bevacizumab dose			Study sample size	Follow-up duration, mo	Quality score
			Control arm	Treatment arm	Bevacizumab dose			
Dotan et al 2012[29]	2	mCRC	Capecitabine, oxaliplatin, + cetuximab	Capecitabine, oxaliplatin, and cetuximab + bevacizumab	7.5 mg/kg × 3 wks	23	26	3
Schmoll et al 2012[30]	3	Advanced CRC	mFOLFOX6 + cediranib	mFOLFOX6 + bevacizumab	5 mg/kg × 2 wks	1422	14	5
Cunningham et al 2013 (1)[18]	3	mCRC	Capecitabine	Capecitabine + bevacizumab	7.5 mg/kg × 3 wks	280	24.8	3
Cunningham et al 2013[31]	2	mCRC	mFOLFOX6 + cediranib	mFOLFOX6 + bevacizumab	10 mg/kg × 2 wks	210	NA	4
Heinemann et al 2014[32]	3	mCRC	FOLFIRI + cetuximab	FOLFIRI + bevacizumab	5 mg/kg × 2 wks	592	33-39	3

bFOL indicates bolus fluorouracil and low-dose leucovorin with oxaliplatin; CapeOx, capecitabine with oxaliplatin; FFG, folinic acid, fluorouracil, and gemcitabine; FOLFIRI, leucovorin calcium (calcium folinate), infusional 5-fluorouracil, and irinotecan; FOLFOX4, fluorouracil/folinic acid and oxaliplatin; IFL, irinotecan, fluorouracil, and leucovorin; mCRC, metastatic colorectal cancer; mFOLFOX6, modified infused fluorouracil and leucovorin with oxaliplatin; mIFL, irinotecan and bolus 5-fluorouracil/leucovorin; NA, not available; XELOX, capecitabine and oxaliplatin.

or placebo chemotherapy regimen for the treatment of CRC were retrieved. To be included, a study was required to have clear clinical data for any TEE (ie, venous thrombosis, arterial thrombosis, thrombosis, pulmonary embolism, cardiac ischemia, cerebral ischemia, cardiac infarction, or cerebral infarction) for the 2 chemotherapy groups. Thus, single-arm or phase 1 RCTs, or review articles were excluded. Also excluded were non-English publications, studies of safety or pharmacokinetics, replies to authors, nonrandomized studies, publications in which TEEs were not reported, and studies in which both arms received bevacizumab therapy.

Quality Assessment

To assess the quality of reporting completeness of each RCT included in our study, we incorporated the Jadad quality assessment criteria.[50] Briefly, this is a test of 5 yes or no questions, in which each question answered "yes" is worth 1 point and no in-between answers are permitted. The answers to the first 3 questions are scored as 1 point if the study was randomized, 1 point if double-blinded, and 1 point if it addressed dropouts; each of these 3 questions is scored as zero points if the answer is "no."

The answers to the last 2 questions are scored as an extra point if the study was randomized and the randomization method was appropriate, and an extra point if the study was double-blinded and the blinding method was appropriate, but 1 point is deducted for each "no" response. Quality scores yielded from these criteria range from zero (very poor quality) to 5 (excellent quality). We conducted a sensitivity analysis by removing studies with poor quality scores (≤2) and recalculated the effect size for each outcome to examine the influence of studies with poor quality scores on our results.

Data Extraction

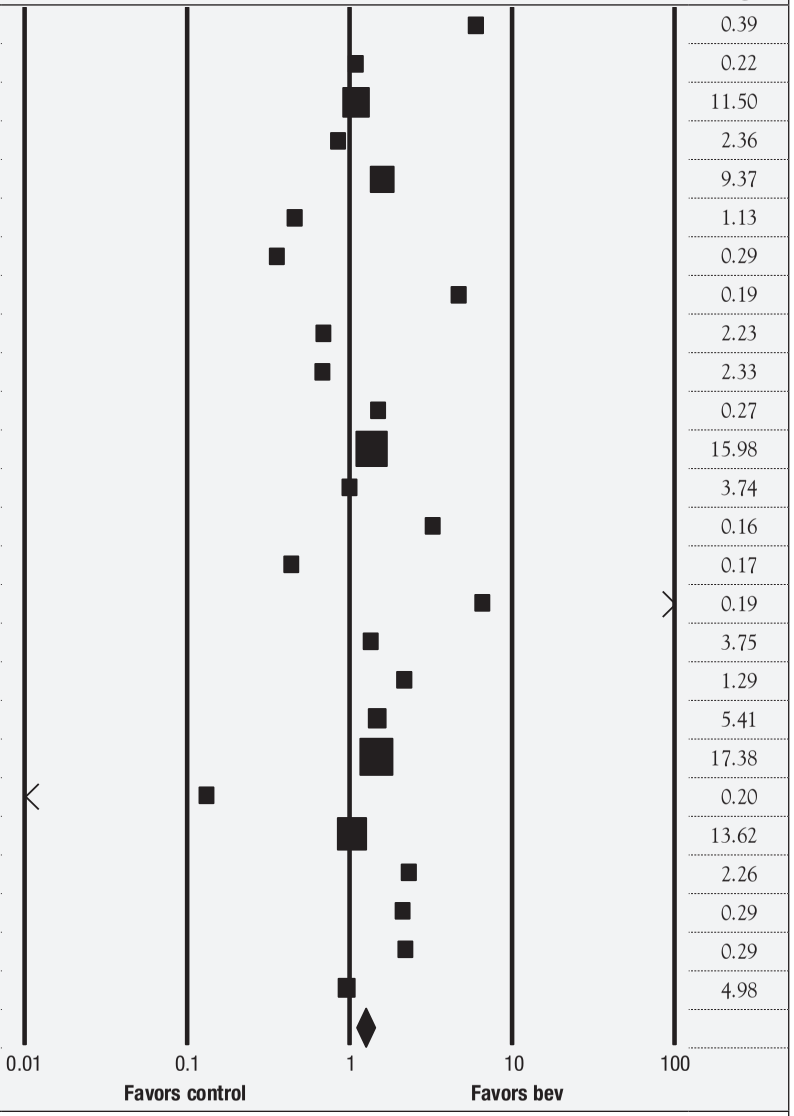
Relevant data (the number or percentage of TEEs and the sample size used for safety analysis in the bevacizumab and the control arms) were extracted from each study individually. Using all these data and a 2 × 2 contingency table, we calculated the risk ratio (RR) of TEEs for each study, along with 95% confidence intervals (CIs). Two blinded reviewers performed all data extraction, as well as the calculation of effect sizes for the 22 RCTs included.

Outcome Definitions Used in This Report

In our study, TEEs were classified into 3 groups. First, overall TEEs were defined as the sum of arterial and venous TEEs reported in each study. Second, venous TEEs were defined as any events involving venous thrombosis, venous thromboembolism, vein occlusion, thrombophlebitis, or pulmonary embolism. Arterial TEEs were defined as any events including arterial thrombosis, car-

Figure 4 Forest Plot of the Effect of Bevacizumab on Venous Thromboembolic Events in Patients with Colorectal Cancer

Clinical trial	Statistics for each study: Risk ratio	Lower limit	Upper limit	Z value	P value	Events/total: Bev arm	Control arm	Relative weight
Kabbinavar et al (A)[11]	6.000	0.761	47.288	1.701	.089	6/35	1/35	0.39
Kabbinavar et al (B)[11]	1.094	0.071	16.771	0.064	.949	1/32	1/35	0.22
Hurwitz et al[12]	1.096	0.751	1.602	0.476	.634	49/393	45/397	11.50
Kabbinavar et al[19]	0.851	0.368	1.965	–0.378	.705	9/100	11/104	2.36
Saltz et al[20]	1.592	1.046	2.422	2.169	.030	54/694	33/675	9.37
Hochster et al (A)[21]	0.460	0.137	1.545	–1.256	.209	4/71	6/49	1.13
Hochster et al (B)[21]	0.357	0.033	3.831	–0.850	.395	1/70	2/50	0.29
Hochster et al (C)[21]	4.699	0.248	88.967	1.031	.302	3/72	0/48	0.19
Jackson et al (A)[22]	0.691	0.292	1.633	–0.843	.399	6/56	21/137	2.23
Jackson et al (B)[22]	0.681	0.294	1.580	–0.895	.371	6/59	21/137	2.33
Sharma et al[23]	1.500	0.127	17.667	0.322	.747	1/4	1/6	0.27
Allegra et al[14]	1.370	0.993	1.889	1.917	.055	84/1326	61/1321	15.98
Tebbutt et al[16]	1.000	0.514	1.944	0.000	1.000	16/157	16/156	3.74
Kemeny et al[24]	3.250	0.137	77.250	0.729	.466	1/35	0/38	0.16
Madajewicz et al (A)[7]	0.439	0.019	10.179	–0.514	.607	0/18	1/24	0.17
Madajewicz et al (B)[7]	6.579	0.335	129.162	1.240	.215	2/18	0/24	0.19
Price et al[17]	1.351	0.696	2.623	0.888	.375	30/315	11/156	3.75
Stintzing et al[26]	2.174	0.701	6.740	1.345	.179	8/46	4/50	1.29
Bennouna et al[27]	1.479	0.851	2.570	1.387	.165	29/401	20/409	5.41
de Gramont et al[28]	1.467	1.078	1.997	2.437	.015	94/1145	63/1126	17.38
Dotan et al[29]	0.132	0.008	2.297	–1.390	.165	0/12	3/11	0.20
Schmoll et al[30]	1.037	0.732	1.469	0.205	.838	59/704	57/705	13.62
Cunningham et al (1)[18]	2.320	0.986	5.458	1.928	.054	16/134	7/136	2.26
Cunningham et al (A)[31]	2.121	0.197	22.846	0.620	.535	2/66	1/70	0.29
Cunningham et al (B)[31]	2.212	0.205	23.836	0.655	.513	2/66	1/73	0.29
Heinemann et al[32]	0.961	0.540	1.709	–0.135	.892	21/295	22/297	4.98
Overall impact	1.244	1.094	1.415	3.330	.001			



Bev indicates bevacizumab; CI, confidence interval.

diac ischemia, cerebral ischemia, cardiac infarction, or cerebral infarction.

Statistical Methods

The RR, 95% CI, and *P* value were calculated for each study. For each outcome, the RR for TEEs was calculated using the fixed-effect model, because the between-study statistical heterogeneity measured by the Higgins I^2 test was <50% and was insignificant. (If the I^2 value is <50%, then a fixed-effect model is considered appropriate; otherwise, a random-effect model should be used.) In addition, we performed 2 forms of sensitivity analysis for each outcome by removing 1 study at a time, as well as studies with poor quality scores (≤2), then we recalculated the fixed-effect estimates.

The presence of publication bias was evaluated visually using a funnel plot of the logarithm of effect size against the standard error for each trial, and statistically using the 2-tailed *P* value results for the Egger's and Begg's tests. If a *P* value showed significance, it would indicate significant publication bias.

The analyses were made using Microsoft Excel 2010 and the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ).

Results

According to our search criteria, 506 potentially relevant clinical trial publications were identified. Of these, 387 articles were excluded, because they were single-arm studies, review articles, abstracts only, or were counted twice (**Figure 1**). A total of 22 RCTs, representing a total of 13,185 patients, were included in our meta-analysis (**Table**).

The numbers of TEEs quantified in this analysis were taken from 7 phase 2, 13 phase 3, 1 phase 2/3, and 1 phase-undetermined RCTs. Of the 22 RCTs, only 4 were placebo-controlled and blinded. The follow-up duration of the studies included ranged from 12 months to 60 months.

The dose of bevacizumab varied between studies—either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. The quality score for each RCT was calculated (see **Appendix, Table 1**, at www.AHDBonline.com), and the majority of studies received a score of 2 or 3. Furthermore, 3 studies had a quality score of 1; 5 studies had a score of 2; 12 studies had a score of 3; 1 study had a score of 4; and 1 study had a score of 5. No study yielded a quality score of zero. (Detailed baseline characteristics of all patients included in each study are presented in the **Appendix, Table 2**, at www.AHDBonline.com.)

Results of Individual Studies

Overall thromboembolic events. We combined the number of arterial and venous events from each trial to analyze the overall risk for TEEs in the bevacizumab and the control groups. All 22 RCTs were included for this outcome assessment, and the events of overall TEEs were developed in 9.9% of bevacizumab-treated patients compared with 7.5% of the control patients. Compared with patients in the control arm, patients receiving bevacizumab plus chemotherapy had a significant risk for TEEs (RR, 1.334; 95% CI, 1.191-1.494; *P* <.001; I^2 = 1.37%; **Figure 2**, available at www.AHDBonline.com).

Sensitivity analysis, by removing 1 study at a time, showed effect sizes ranging from an RR of 1.305 (95% CI, 1.163-1.464; *P* <.001) to an RR of 1.374 (95% CI, 1.219-1.549; *P* <.001). In addition, an effect size of RR of 1.305 (95% CI, 1.141-1.493; *P* <.001) was yielded by removing studies with a poor quality score (≤2).

For overall TEEs, visual evaluation of the funnel plot (**Figure 3**, available at www.AHDBonline.com) of logarithm of effect sizes versus standard error for each trial indicated some publication bias. However, the *P* values of Egger's and Begg's tests were 0.968 and 0.967, respectively. Thus, there was no significant evidence of publication bias for studies included in the assessment of overall TEEs.

Venous TEEs. For patients with CRC included in this analysis, venous TEEs were observed in 8% of patients receiving bevacizumab plus chemotherapy compared with 6.5% of the control group. According to our results, the RR for venous TEEs in the bevacizumab group versus the control group was 1.244 (95% CI, 1.091-1.415; *P* = .001; I^2 = 0.0%; **Figure 4**). Significant risk for venous TEEs was observed even after removing (a) all studies with quality score ≤2 (RR, 1.258; 95% CI, 1.079-1466; *P* = .003) and (b) 1 study at a time (ie, range of RR of 1.202 [95% CI, 1.043-1.384; *P* = .011] to 1.280 [95% CI, 1.115-1.470; *P* <.001]).

For publication bias, **Figure 5** (available at www.AHDBonline.com) shows the funnel plot of the logarithm of effect sizes against the standard error for each study included in this outcome, except for 1 missing study; however, the results of Egger's and Begg's tests were 0.877 and 0.855, respectively. Therefore, no significant publication bias was present.

Arterial TEEs. Among the RCTs in which any arterial TEE was reported for patients with CRC, the percentage of arterial TEEs was 2.3% for bevacizumab chemotherapy and 1.1% for the control therapy. The estimated RR of having an arterial TEE for bevacizumab versus the control therapy was 1.627 (95% CI, 1.162-2.279; *P* = .005; I^2 = 0.0%; **Figure 6**). Sensitivity analysis, by deleting a single study at a time, showed that RR point estimates ranged from 1.561 (95% CI, 1.112-2.192; *P* = .010) to 1.772 (95% CI, 1.177-2.666; *P* = .006). Similarly, a significant RR of 1.631 (95% CI,

Figure 6 Forest Plot of the Effect of Bevacizumab on Arterial Thromboembolic Events in Patients with Colorectal Cancer

Clinical trial	Statistics for each study: Risk ratio	Lower limit	Upper limit	Z value	P value	Events/total: Bev arm	Control arm	Relative weight
Kabbinavar et al (A)[11]	0.333	0.014	7.913	–0.680	.497	0/35	1/35	1.13
Kabbinavar et al (B)[11]	2.188	0.208	22.985	0.652	.514	2/32	1/35	2.05
Kabbinavar et al[19]	2.080	0.737	5.872	1.383	.167	10/100	5/104	10.54
Giantonio et al[13]	2.250	0.250	20.260	0.723	.470	3/287	1/285	2.35
Saltz et al[20]	1.667	0.660	4.210	1.082	.279	12/694	7/675	13.23
Allegra et al[14]	1.357	0.748	2.461	1.005	.315	25/1326	18/1321	32.03
Tebbutt et al[16]	15.034	0.867	260.796	1.862	.063	7/157	0/156	1.39
Madajewicz et al (B)[7]	1.333	0.089	19.911	0.209	.835	1/18	1/24	1.55
Price et al[17]	26.332	1.615	429.266	2.297	.022	26/315	0/156	1.46
Guan et al[25]	1.500	0.062	36.356	0.249	.803	1/141	0/70	1.12
Bennouna et al[27]	0.765	0.172	3.396	–0.352	.725	3/401	4/409	5.11
de Gramont et al[28]	1.520	0.715	3.230	1.088	.277	17/1145	11/1126	19.97
Cunningham et al (1)[18]	2.030	0.518	7.950	1.016	.309	6/134	3/136	6.09
Heinemann et al[32]	2.014	0.184	22.086	0.573	.567	2/295	1/297	1.98
Overall impact	1.627	1.162	2.279	2.831	.005			

Bev indicates bevacizumab; CI, confidence interval.

1.057-2516; P = .027) was observed after deleting poor-quality studies.

Figure 7 (available at www.AHDBonline.com) shows the funnel plot of the logarithm of effect sizes versus standard error for studies that included arterial TEEs, which indicates some bias. However, the 2-tailed P values for Egger's and Begg's tests (0.702 and 0.207, respectively) showed no significant evidence of publication bias for this outcome.

Discussion

In this meta-analysis we considered the risk for overall, arterial, and venous TEEs associated with the use of bevacizumab chemotherapy in patients with CRC based on 22 RCTs comparing bevacizumab therapy and a controlled group.[7,11-14,16-32] Our findings indicate a significant increase in risk for TEEs in this particular population. Patients with CRC who received bevacizumab had a >33% risk for any type of thrombosis. More precisely, bevacizumab therapy was associated with a 24% increased risk for venous TEEs and a 62% increased risk for arterial TEEs.

We believe that our study is unique, because it focused on comprehensively addressing the risk for TEEs in bevacizumab-treated patients with CRC using more recent and a larger number of RCTs than in a previous pooled meta-analysis. Our results are in agreement with those of previous pooled analyses that included patients with CRC in terms of significant overall risk for TEEs,[44-48] significant arterial risk,[35,37,38,49] and significant risk for grade ≥3 venous TEEs.[33] However, our findings for venous TEEs conflict with results of previous studies. The RR estimated by Nalluri and colleagues for all grades of venous TEEs in patients with CRC was 1.19 (95% CI, 0.92-1.55).[33] By contrast, Scappaticci and colleagues[34] reported a lower hazard ratio (HR) of venous TEE risk (HR, 0.89; 95% CI, 0.66-1.20; P = .44). The results of Hurwitz and colleagues regarding venous TEEs in CRC indicated a nonsignifi-

cant unadjusted odds ratio (OR) of 1.22 (95% CI, 0.93-1.58).[36] Similarly, Galfrascoli and colleagues found a nonsignificant RR of 1.23 (95% CI, 0.93-1.62; *P* = .15) for venous TEEs in patients with CRC.[49]

Some reasons can explain these conflicts. First, the number of CRC clinical trials included in previous reports was smaller (3,[33] 4,[36] and 6[49]) than in our analysis (22 RCTs). Therefore, the pooled sample size of those studies was also small, ranging from 1096 to 2813 patients. It has been proved that a negative correlation exists between sample size and CI limits; thus, the smaller the sample size, the wider the "certain" level of confidence, and vice versa.[51] Furthermore, the focus of the studies by Scappaticci and colleagues[34] and Galfrascoli and colleagues[49] was limited to grade ≥3 TEEs (other grades were omitted), which would explain the difference between their findings and ours.

Although the previous pooled studies did not have the power to generate statistical significance, an increased risk (ie, 9%-19%) for venous TEEs was reported for patients with CRC.[33,36,49] Similarly, for bevacizumab-treated patients with CRC in our analysis, the risk for venous or arterial thrombosis was more than 24% and 62% higher, respectively, than in control patients. Because cancer-related thrombosis is the second leading cause of death among patients with cancer, and is associated with substantial mortality risk (OR, 8.1; 95% CI, 3.6-18.1),[40,41,52] we believe that the increased risk observed in previous and current studies indicates the presence of a clinical issue that warrants greater awareness to help control its consequences.

The mechanism by which bevacizumab causes thrombosis is still unknown, but several theories have been proposed. Those theories are based on the pathologic impact of VEGF inhibition accomplished by bevacizumab.[33,37] One theory proposed that hindering the physiologic anti-inflammatory effect of VEGF would increase vascular inflammation and cause thrombus development eventually.[33,35,37] In addition, the inhibition of VEGF would decrease the production of nitric oxide and prostacyclin, leading to increased blood viscosity and platelet aggregation.[33,35,37] Others have suggested that bevacizumab interaction with malignant cells produces toxic substances that increase blood coagulation.[33] Some investigators have connected the anti-VEGF activity of bevacizumab to damaging the endothelial walls of blood vessels and exposing subendothelial lipids by thrombosis formulation.[33,38]

Our findings are of considerable importance for CRC management and cautious prescribing of bevacizumab for patients with CRC, because cancer is already a risk factor for TEEs. Therefore, taking into account how much prescribing bevacizumab for patients with CRC can induce TEEs, and suitable prophylaxis are advised.[41,43,52] In a large study, patients with CRC had a 3.1% incidence of venous TEEs over the 2-year follow-up.[53]

In addition, patients with metastatic cancer who receive chemotherapy have been proved to have a more than 6-fold increased risk for thrombosis compared with patients with cancer who do not receive chemotherapy.[54] Therefore, we believe that identifying drugs linked to TEEs is the first step in preventing such adverse effects and will lead to better outcomes. The significant risk presented in our study will increase the awareness of this issue, which may lead to better diagnosis and management of TEEs in patients with CRC who receive this drug.

Patients with cancer who have a history of thrombosis[52] or previous exposure to chemotherapy,[41,55] and patients who are undergoing major surgery,[56] hospitalized,[55] or newly diagnosed[54] have an increased risk for TEEs and should receive thromboprophylaxis appropriately. However, the 2014 updated guideline of the American Society of Clinical Oncology does not recommend prescribing thromboprophylaxis for outpatients. Interestingly, this guideline mandates low-molecular-weight heparin or low-dose aspirin as prophylaxis for patients with multiple myeloma who receive antiangiogenesis treatment, such as bevacizumab.[57] We found that patients with metastatic CRC who receive bevacizumab plus chemotherapy are at increased risk for TEEs and, similar to multiple myeloma, our results may support the need to consider thromboprophylaxis for patients with CRC.

Thromboprophylaxis is recommended by the American College of Chest Physicians guidelines for acutely admitted patients with any type of cancer[58]; however, some survey studies have proved that thromboprophylaxis is underutilized by most oncologists because of unawareness of these guidelines, omitted risk factors, and caution of associated adverse events.[58,59] To better minimize the mortality risk associated with cancer-related thrombosis, primary prophylaxis therapy should be considered for all patients at risk.[60] Bevacizumab is known to cause bleeding and thrombocytopenia,[11-14,16-32] and the potential benefit of using aspirin or other anticoagulants in clinical trials has not been proved to outweigh the risk.[49,60] Therefore, a careful and patient-tailored thromboprophylaxis guideline for bevacizumab use in CRC is greatly needed.

Our analysis has some strengths over previous studies. This is the first analysis of the risk for overall, venous, and arterial TEEs associated with bevacizumab that is focused solely on patients with CRC. Our specific focus on patients with CRC eliminated the confounding effect of cancer type, an important factor contributing to the associated risk. Moreover, we analyzed 22 RCTs, including the most recent trials. This produced a larger pooled sample size than in previous meta-analyses, thereby providing adequate power to detect potentially modest effects.

Limitations

Although our study has many strengths, it has several limitations as well. First, we did not analyze the impact of different bevacizumab doses and heterogeneous chemotherapy regimens on the development of TEEs. Therefore, we do not know if a subgroup analysis of those regimens would alter the significance of our findings.

Second, because we did not have access to all patient characteristics and confounding factors, it is possible that some TEEs in the RCTs analyzed might be attributable to factors other than bevacizumab itself. Although our study included RCTs analyzed in previous meta-analyses,[33-38,44-49] those meta-analyses reported event and sample numbers that are different from our findings. Possible reasons for this discrepancy include that those analyses might have had different definitions for TEEs, or they might have contacted the authors of the original RCTs for clarification and/or supplemental data.

Therefore, based on our definition of TEEs, and because we did not contact the authors of the RCTs for clarification, our numbers are not the same as those presented in previous meta-analyses.

Conclusion

The findings of our study indicate that the risk for thrombotic events, either venous or arterial, is associated with the combination of bevacizumab and chemotherapy in patients with CRC. To better understand this association and improve patient outcomes, additional studies are needed. The evaluation of bevacizumab and TEEs should consider the grade of TEEs and the impact of different bevacizumab doses, and it should stratify the results by chemotherapy regimens. Further investigation to understand the mechanism by which bevacizumab leads to TEEs in patients with CRC, and to identify the best prophylaxis, is recommended. Prolonged observational studies that can control confounding factors, identify patients at risk, determine higher-risk chemotherapy combinations, and provide evaluation based on real-world data are also needed. Healthcare providers are encouraged to consider the use of a thrombosis prophylactic regimen, including periodic monitoring of their patients and careful management of those at higher risk for thrombosis. ■

Author Disclosure Statement

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Stakeholder Perspective next page

STAKEHOLDER PERSPECTIVE

Better Patient Education Needed Regarding Thromboembolic Events Risk in Patients with Cancer

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Educating patients on the risks of their treatments in the context of their medical condition is challenging. Physicians need data from randomized, real-world, observational clinical trials to effectively assess a drug's benefits and risks for specific patient subgroups based on age, concomitant medications, and specific cancers.

Meta-analyses provide healthcare professionals information that can be used to assess the risks and benefits of current treatments for specific conditions. Alahmari and colleagues present a meta-analysis of randomized controlled trials (RCTs) on thromboembolic events associated with bevacizumab plus chemotherapy in patients with colorectal cancer (CRC).[1] Their meta-analysis is a great resource for healthcare professionals and for associations that generate treatment guidelines and prophylaxis recommendations to avoid adverse events. This is a valuable resource for clinicians. Similar evidence for other cancers is needed to guide clinical practice and reduce adverse events.

PATIENTS: Patients with cancer are at an increased risk for thromboembolic events.[2] A patient's age, sex, ethnicity, and treatments, and the impact of cancer on blood coagulation affect the risk for such events.[2] Patients can struggle to understand the risks and benefits of a treatment, especially in complex medical conditions such as CRC. They need to know their risk for thromboembolic events, especially with metastatic CRC, and the potential risks of various CRC treatments, which include combination regimens. Alahmari and colleagues found a significant risk for thromboembolic events in patients with CRC who receive bevacizumab.[1] This implies an increased need for thromboprophylaxis agents and for recognizing the signs and symptoms of venous thromboembolism (VTE). To add to the complexity, patients with cancer are also at risk for bleeding, so they need to know the risks for bleeding associated with anticoagulant treatment.[2]

Physicians are beginning to use icon arrays to depict clinical risks for educating patients, and this needs to be more common: many patients with cancer receive limited information on deep-vein thrombosis (DVT) or pulmonary embolism (PE) risks. Aggarwal and colleagues surveyed 500 patients with cancer about DVT/PE risks.[3] Only 24% and 15% of patients had heard of DVT and PE, respectively; only 19% and 17% could list the symptoms; and only 3% knew that cancer treatments carry a risk for DVT/PE.[3] Most alarming: only 25% of patients had received education about DVT/PE prevention, and <50% had received VTE prophylaxis.[3]

MANUFACTURERS/PAYERS: The pharmaceutical industry provides safety information from RCTs as part of a drug label through postmarketing pharmacovigilance and long-term extension safety trials. However, RCT data are captured in controlled settings and may not reflect patients in real-world settings who may receive additional treatments for their comorbidities. Data from various registries are critical for providing real-world data. Payers can play a critical role in leveraging their claims data to supplement RCTs data for further insights into the incidence of VTE events. Electronic medical records could be used to detect whether at-risk patients have received VTE prophylaxis and have been educated on VTE and bleeding risks. Payers' increased capability in predictive analytics further offers an opportunity to identify patients at risk.

PROVIDERS: Explaining risks to patients is difficult, and takes time. Patients require ongoing education on their prescribed treatment, emphasizing the need for continuing education beyond office visits. For many cancer treatments, specialty pharmacy call center clinicians play an important role in patient education through monthly outbound telephonic support. Interactive multimedia education and icon arrays that graphically explain treatment risks offer opportunities to improve the process. Providers can assist by conducting studies to add to the literature. Quick online access to updated guidelines would be a great improvement. Representation from the cardiology and vascular communities to assist oncologists in developing guidelines for VTE prevention in specific cancers, along with patient recommendations, would further enhance outcomes. ■

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